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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

DATE: April 2, 2004

SUBJECT: Office of Pesticide Programs Health Effects Division Evaluation of the Triazolealanine Group Report *Profile of the Triazole-derivative Fungicide Compounds and their Common Metabolites.*
DP Barcode: D280913 MRID: 45575501
Decision No.: 301646

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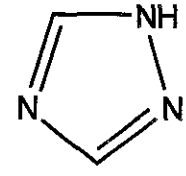
Background

In August of 2000, the Agency imposed a moratorium on the registration of fungicides belonging to the triazole class due to concerns regarding 1,2,4-triazole (pictured at right). In order to address the concerns surrounding the triazole-derived fungicides, the industry task force known as the Triazolealanine Group (TAG) submitted, in January 2002, a report titled the *Profile of the Triazole-derivative Fungicide Compounds and their Common Metabolites* (MRID 45575501). The TAG report, also known as the Omnibus Report, includes a summary of residue chemistry data that were available at the time of its compilation and presents an aggregate acute dietary risk assessment for 1,2,4-triazole. The TAG assessment reports triazole exposure estimates that are less than 3% of the acute reference dose for all population subgroups. This memorandum is the Agency's evaluation of the TAG report. Due to outstanding questions regarding 1,2,4-triazole toxicity, this evaluation focuses on the residue chemistry information and assumptions regarding the exposure elements of the aggregate dietary risk assessment performed by the TAG.



1,2,4-triazole

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Summary of Available Residue Data

With respect to 1,2,4-triazole, the TAG has confirmed that the Agency has all known residue chemistry data owned by the members of the group for parent fungicides having registered uses. The TAG makes no claims regarding data from non-group members or from studies on unregistered triazole-derived fungicides that have not been submitted to the Agency. The TAG has not taken non-member or non-submitted data into consideration in the analysis presented in its Omnibus Report.

Plant Metabolism of Triazole-derived Fungicides. Data from studies investigating the nature of the residues in plants treated with triazole-derived fungicides show that in most cases, 1,2,4-triazole is rapidly conjugated with serine to form triazolealanine (TA). The TA can then be further metabolized to form triazoleacetic acid (TAA). Free triazole may be formed in the environment. In rotational crop studies, however, few matrices showed the presence of 1,2,4-triazole and TA/TAA predominated. Presumably, any free triazole that was taken into the rotated crops was quickly conjugated to form TA and TAA. The available plant metabolism data are summarized in Table 1.

Table 1. Summary of Occurrences of Free and Conjugated 1,2,4-Triazole in Plants.[A]

Statistic	1,2,4-Triazole	Triazolealanine	Triazoleacetic Acid	Triazolyllactic Acid or Triazolepyruvic Acid
Primary Crops				
n (total)	79	79	80	50
n (≥ LOD)	11 (14%)[B]	43 (54%)	28 (35%)	7 (14%)
n (< LOD)	28 (35%)	11 (14%)	15 (19%)	14 (28%)
n (No Data)[C]	40 (51%)	25 (32%)	37 (46%)	29 (58%)
Rotational Crops				
n (total)	123	123	123	53
n (≥ LOD)	14 (11%)	58 (47%)	44 (36%)	30 (57%)
n (< LOD)	69 (56%)	31 (25%)	45 (37%)	9 (17%)
n (No Data)[C]	40 (33%)	34 (28%)	34 (27%)	14 (26%)

[A] Taken from MRID 45575501, p. 18.
[B] Percent of occurrence
[C] No Data indicates that the compounds addressed in the table columns were not reported, not looked for, and/or not identified.

Livestock Metabolism of Triazole-derived Fungicides. 1,2,4-triazole has been shown to be a major residue (>10% of the total radioactive residue) in rat, goat, cattle, and poultry matrices. The conversion of parent fungicide to 1,2,4-triazole is quite variable, ranging from approximately 5% to 70%. The in-situ formation of 1,2,4-triazole appears to be primarily dependent on the nature of the parent compound. Once formed, 1,2,4-triazole tends to partition into the muscle, kidney, and milk/egg commodities.

Assumptions in the TAG Cumulative Dietary Risk Assessment and Agency Comments

Parent Compound Residue Level. The TAG assessment used the highest tolerance level of any triazole-derived fungicide for each commodity in their assessment. The TAG believes that this results in a very conservative estimate of parent compound residue levels.

Agency Comment: Using the highest tolerance level for each food does result in a very highly conservative estimate of parent residue provided that (1) the applied fungicide is the only significant source of 1,2,4-triazole and that (2) the highest tolerance for a given food is significantly higher than the majority of the other triazole-derivative fungicide tolerances. Regarding sources, prior to conducting its own aggregate assessment, the Agency will investigate the labeling of all triazole-derived fungicides to ensure that the use restrictions preclude application of other triazole-derived fungicides for the extent of the crop growing season. If such restrictions are not in place, then the assumptions regarding parent fungicide residue levels will need to be revised upwards to maintain the currently assumed degree of conservatism. With respect to the range of tolerance values, triazole-derivative fungicide tolerances are quite varied on most commodities. Therefore, selection of the highest tolerance value for a given commodity for use throughout the assessment does result in a highly conservative estimate of triazole residues. The Agency further notes that the use of 100% crop treated in the TAG assessment also results in highly conservative estimates of residues.

Molecular Weight Conversion of Parent Triazole-derived Fungicide Levels to 1,2,4-Triazole. As noted above, the TAG assessment used the maximum triazole-derived fungicide tolerance level for each commodity as the initial residue level. That residue level was then converted to 1,2,4-triazole using a molecular weight conversion factor of 0.24. Use of that factor for all triazole-derived fungicides results in a more conservative estimate than parent-compound-specific factors (Table 2).

Table 2. Summary of Triazole-derived Fungicide to 1,2,4-Triazole Molecular Weight Conversion Factors.[A]

Compound	Molecular Weight	Conversion Factor[B]
1,2,4-Triazole	69.07	1.00
Bitertanol	337.42	0.20
Cyproconazole	291.78	0.24
Epoxiconazole	329.76	0.21
Flusilazole	315.39	0.22
Propiconazole	342.22	0.20
Tebuconazole	307.82	0.22
Hexaconazole	314.21	0.22
Fenbuconazole	336.82	0.21
Myclobutanil	288.78	0.24
Triadimefon	293.75	0.24

Compound	Molecular Weight	Conversion Factor[B]
Triadimenol	295.76	0.23
Difenoconazole	406.26	0.17
Tetraconazole	372.15	0.19
Paclobutrazole	293.79	0.24

[A] Taken from MRID 45575501, p. 248.
[B] Mol. Wgt. 1,2,4-Triazole ÷ Mol. Wgt. Parent Compound

Agency Comment: The Agency agrees that the use of the 0.24 molecular weight conversion factor results in more conservative estimates of 1,2,4-triazole residue estimates than the use of parent-compound-specific factors. Given that the conversion factors range from 0.17 to 0.24 and that most are greater than 0.20, the Agency notes that the use of this factor does not result in overly conservative conversion of parent compound to 1,2,4-triazole as a whole.

Metabolic Conversion of Parent Triazole-derived Fungicide Levels to 1,2,4-Triazole. The TAG assessment used the maximum % total radioactive residue (TRR), rounded up to the nearest 5%, to account for the degree of conversion of parent compound to 1,2,4-triazole. The metabolic conversion factors were obtained from the various primary crop metabolism studies, confined rotational crop studies, and livestock metabolism studies. For crops, a universal metabolism factor of 0.20 was applied; for livestock matrices, commodity-specific conversion factors were used (Table 3).

Table 3. Summary of Parent Triazole-derived Fungicide to 1,2,4-Triazole Metabolic Conversion Factors.[A]

Commodity	Maximum Observed % TRR	Conversion Factor in Assessment
All Plant Commodities	17	0.20
Ruminant Muscle	84.6	0.85
Ruminant Kidney	58.1	0.60
Ruminant Liver	12.6	0.15
Ruminant Fat	20.3	0.25
Milk	81.9	0.85
Poultry Muscle	34.2	0.35
Poultry Kidney	6.9	0.10
Poultry Liver	15.3	0.20
Poultry Fat	0.9	0.05
Egg	67.7	0.70

[A] Adapted from MRID 45575501, p. 247.

Agency Comment: The Agency agrees that the use of the factors listed in Table 3 is appropriate for making conservative estimates of the direct dietary exposure to 1,2,4-triazole, especially the use of the 20% factor for all plant commodities. However, the TAG assessment does not take into account the indirect dietary exposure that will likely

occur from the conversion of parent triazole-derived fungicides to 1,2,4-triazole within the human body. It is unclear at this time how much this omission impacts the overall nature of the TAG assessment.

Agency Conclusion

The TAG report is a very useful reference regarding our state of knowledge of human dietary exposure to 1,2,4-triazole. The report includes an acute aggregate dietary exposure assessment that is intended to provide high-end estimates of exposure based on conservative assumptions regarding residue levels and transformation of parent fungicide to free triazole in plant and livestock commodities. The TAG assessment, however, does not address the in-situ conversion of triazole-derived fungicides to 1,2,4-triazole that may occur in humans following consumption of foods bearing residues of parent fungicide. As such, their assessment may not be as conservative as the group believes. The Agency will be completing an aggregate assessment for the triazole fungicides, at which time this issue, as well as the overall conservatism of the assessment will be addressed.

cc: M. Doherty, RAB2 Reading File

RDI: MADoherty (2/24/04), RALoranger (3/25/04)

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